damage with persistently increased enzymes occurred.

The need for accurate diagnosis, appropriate selection of dosage and careful monitoring of patients taking lithium is stressed.

Familiarity with the pharmacology and toxicology of lithium is a matter of considerable importance. The potential toxicity of lithium and its narrow therapeutic-toxic range have been discussed.

REFERENCES

1. Schou M: Lithium in psychiatry, *In* Etron DH (Ed): Psychopharmacology—A Review of Progress, 1957-1967. Public Health Service Publication No. 1836, US Department of Health, Education, and Welfare, 1968, pp 701-718
2. Fieve RR: Overview of therapeutic and prophylactic trials with lithium in psychiatric patients, chap 16, *In* Gershon S, Shopsin B (Eds): Lithium: Its Role in Psychiatric Research and Treatment. New York, Plenum Press, 1973, pp 317-350
3. Warick LH: Lithium carbonate in the treatment and prophylaxis of recurrent affective disorders: Long term follow-up. Bull Los Angeles Neurol Soc 35:169-180, Oct 1970
4. Warick LH: Lithium salts in the treatment of manic states. Dis Nerv Systm 27:527-530, 1966
5. Spring GK: Hazards of lithium prophylaxis. Dis Nerv Systm 35:351-354, 1974
6. Corcoran AD, Taylor RD, Page IH: Lithium poisoning from the use of salt substitutes. JAMA 139:685-688, 1949
7. Cleveland SA: A case of poisoning by lithium. JAMA 60: 722, Mar 8, 1913
8. Schou M, Amdisen A, Trap-Jensen J: Lithium poisoning. Am J Psychiat 125:520-527, 1968
9. Von Hartizsch B, Hoenich NA, Leigh RJ, et al: Permanent neurologic sequelae despite hemodialysis for lithium intoxication. Br Med J 4:757-759, 1972
10. Himmelhoch JM, Mulla D, Neil JF, et al: Incidence and significance of mixed affective states in a bipolar population. Arch Gen Psych 33:1062-1068, Sep 1976
11. Shopsin B, Johnson G, Gershon S: Neurotoxicity with lithium: Differential drug responsiveness. Int Pharmacopsychiat 5: 170-182, 1970
12. Quitkin FN, Rifkin A, Klein DF: Lithium in other psychiatric disorders, chap 15, *In* Gershon S, Shopsin B (Eds): Lithium: Its Role in Psychiatric Research and Treatment. New York, Plenum Press, 1973, pp 295-306
13. Small J, Kellams J, Milstein V: A placebo controlled study of lithium combined with neuroleptics in chronic schizophrenic patients. Am J Psychiat 132:1315-1317, Dec 1975
14. el-Guebaly N: Manic-depressive psychosis and drug abuse. Can Psychiat Assoc J 20:595-598, Dec 1975
15. Mendels J: Lithium in the treatment of depression. Am J Psychiat 133:373-378, Apr 1976
16. Shopsin B, Gershon S: Pharmacology-toxicity of the lithium ion, chap 7, *In* Gershon S, Shopsin B (Eds): Lithium: Its Role in Psychiatric Research and Treatment. New York, Plenum Press, 1973, pp 107-146
17. Peters MA: Lithium intoxication producing chorea athetosis with recovery. Wisconsin Med J 48:1075-1076, 1949
18. Vacaflor L: Lithium side effects and toxicity: The clinical picture, chap 13, *In* Johnson FN (Ed): Lithium Research and Therapy. New York, Academic Press, 1975, pp 211-225
19. Segal RL, Rosenblatt S, Eliasoph I: Endocrine exophthalmus during lithium therapy of manic-depressive disease. N Engl J Med 289:136-138, 1973
20. Johnson S: The effects of lithium on basic cellular processes, chap 33, *In* Johnson FN (Ed): Lithium Research and Therapy. New York, Academic Press, 1975, pp 533-554
21. Lieber CS: The metabolism of alcohol. Scientific Am 234: 25-33, 1976
22. Ban TA (Ed): The benzodiazepines, chap 17, *In* Psychopharmacology. Baltimore, Williams & Wilkins Co, 1969
23. Thomsen K, Schou M: The treatment of lithium poisoning, chap 14, *In* Johnson FN (Ed): Lithium Research Therapy. New York, Academic Press, 1975, pp 227-236
24. Elizur A, Shopsin B, Gershon S, et al: Intra-extra cellular lithium ratios and clinical course in affective states. Clin Pharmacol Ther 13:947-952, 1972
25. Frazer A, Mendels J, Secunda SK, et al: The prediction of brain lithium concentrations from plasma or erythrocyte measures. J Psychiat Res 10:1-7, 1973
26. Mendels J, Frazer A: Intracellular lithium concentration and clinical response: Towards a membrane theory of depression. J Psychiat Res 10:9-18, 1973

Refer to: Heffner J, Starkey T, Anthony P: Salicylate-induced noncardiogenic pulmonary edema. West J Med 130:263-266, Mar 1979

Salicylate-Induced Noncardiogenic Pulmonary Edema

JOHN HEFFNER, MD
Oceanside, California

THOMAS STARKEY, MD
PAUL ANTHONY, MD
Denver

SEVERAL DRUGS when ingested in therapeutic or toxic amounts are known to precipitate noncardiogenic pulmonary edema.[1-6] Prostigmine[1] and alloxan[2] are two agents capable of producing this clinical syndrome in normally prescribed dosages, while heroin,[3] barbiturates,[4] propoxyphene[5] and methadone[6] have varying incidences of pulmonary edema when taken as overdoses.

There have been reports that salicylates may induce pulmonary edema when taken in toxic amounts.[7-9] This association, however, is poorly recognized. Recent editions of textbooks of medicine[10] and pharmacology[11] fail to mention noncardiogenic pulmonary edema as an initial manifestation of salicylate poisoning. Part of the reason may be that the case reports supporting this relationship have seldom ruled out a subtle cardiac cause of pulmonary congestion; hemodynamic data are documented in only one report thereby establishing normal pulmonary vascular pressures.[9]

We report here another case of salicylate toxicity presenting with pulmonary edema. Swan-Ganz catheter data excluded a cardiac cause. We suggest that this aspect of salicylism receive greater recognition to insure early diagnosis and prompt therapy.

Report of a Case

The patient was a 69-year-old man brought to the emergency room confused and severely short of breath. From his friends it was learned

From the Department of Medicine, University of Colorado Medical Center, and the Denver General Hospital, Denver.

Submitted March 10, 1978.

Reprint requests to: John E. Heffner, MD, 3231 Waring Court, Suite O, Oceanside, CA 92054.

that he had been in poor health for three weeks, complaining of weakness and malaise, and had remained in bed with little food intake. During the 12 hours before admission, shortness of breath rapidly developed followed by dizziness, diaphoresis, and confusion. The patient said he had had no chest pain, symptoms of congestive heart failure, palpitations, loss of consciousness or choking episodes, and had not ingested any drug or toxin including ethanol, methanol, ethylene glycol and salicylates. He was a reformed alcoholic and had smoked two packs of cigarettes a day for 50 years.

On physical examination the patient was noted to be hyperpneic, respirations were 30 per minute, pulse was 102 beats per minute, blood pressure was 142/70 mm of mercury and temperature taken rectally was 37.9°C (100.2°F). He was oriented to time and person only. His chest symmetrically expanded with bibasilar rales and wheezes more notable on the right without evidence of consolidation. Findings on cardiac examination were unremarkable with normal venous pulsations.

Laboratory studies gave the following results: serum sodium, 140 mEq per liter; serum potassium, 3.4 mEq per liter; serum chloride, 114 mEq per liter; serum bicarbonate, 7.9 mEq per liter; serum glucose, 115 mg per dl; blood urea nitrogen, 41.8 mg per dl; creatinine, 1.5 mg per dl; serum acetone, negative; prothrombin time, 13 seconds with a 11.5 second control; serum hemoglobin, 16 grams per dl; leukocyte count, 12,100 cells per cu mm with a normal differential count; platelets, normal by smear; erythrocyte sedimentation rate, 3 mm per hour. Arterial blood gas studies (Denver elevation) showed a pH of 7.43, oxygen pressure (P_{O_2}) of 31 mm of mercury and a carbon dioxide pressure (P_{CO_2}) of 13 mm of mercury on room air. After placement of nasal prongs with 4 liters per minute oxygen flow, the blood gas values improved with a pH of 7.48, a P_{O_2} of 82 mm of mercury and a P_{CO_2} of 13 mm of mercury.

Serum albumin was 4 grams per dl; hematest of stool was negative; expectorated sputum Gram stain and culture showed no pathogens; blood cultures were without growth; results of thyroid function tests were within normal limits. A serum salicylate level in a specimen drawn nine hours after the patient presented to the emergency room was 54 mg per dl. A blood and urine toxicology screen was otherwise negative. The cerebrospinal fluid was clear and contained no leukocytes, 30 red cells and normal levels of glucose and protein. The cerebrospinal fluid salicylate level (obtained within one hour of the blood level) was 21 mg per dl. An analysis of urine showed 1+ ketonuria; the electrocardiogram was normal except for sinus tachycardia; a radiograph of the chest showed bilateral alveolar infiltrates compatible with pulmonary edema (Figure 1).

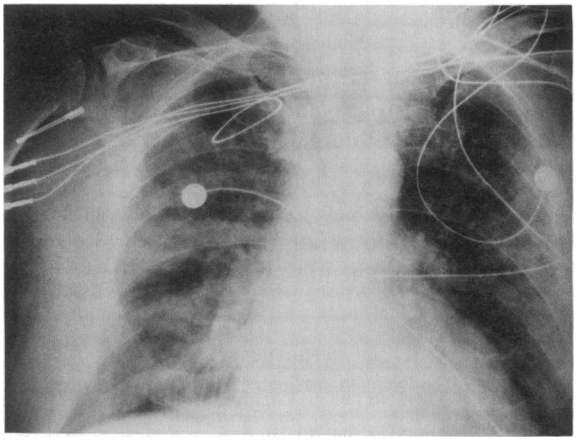

Figure 1.—Radiograph of the chest in a patient with pulmonary edema due to salicylate toxicity.

A Swan-Ganz catheter was inserted into the pulmonary artery and the following initial pressures were obtained: pulmonary artery (PA) systolic pressure of 36 mm of mercury, PA diastolic pressure of 12 mm of mercury and a pulmonary capillary wedge (PCW) pressure of 3 mm of mercury.

Noncardiogenic pulmonary edema secondary to salicylate toxicity was diagnosed and forced alkaline diuresis was initiated. Vitamin K (10 mg) was given intravenously. Fluid therapy during the first 24 hours consisted of 4.4 liters of 5 percent dextrose and 0.45 percent saline, 176 mEq of sodium bicarbonate, and 120 mEq of potassium chloride. Urinary output during this period was 2.6 liters, and the pulmonary artery pressures were unchanged until 24 hours into therapy when the PA systolic pressure was 44 mm of mercury, the PA diastolic pressure was 18 mm of mercury and the PCW pressure was 5 mm of mercury. Administration of ampicillin (1 gram given intravenously every four hours) and gentamicin (100 mg given intravenously every 12 hours) was started empirically on admission but was stopped after 24 hours when cultures were negative.

This therapy resulted in a salicylate level of 29 mg per dl 24 hours after admission, falling to 16

mg per dl the following day. Coincident with the fall in salicylate level was clearing of the pulmonary edema and improvement of the arterial blood gas values to a pH of 7.43, a Po_2 of 76 and a Pco_2 of 24 on room air five days after admission. There was no electrocardiographic or creatine phosphokinase enzyme evidence for a myocardial infarction. A computerized axial tomographic scan of the head showed no abnormalities.

When the patient's mental status improved, he admitted to taking six to eight aspirins a day for multiple complaints but in the last two weeks had taken them "by the handful" because of increasing fatigue.

Discussion

The association of salicylates with pulmonary edema was first noticed in patients with rheumatic heart disease[12,13] and later in patients with normal cardiac function.[7-9,14] Reid noted that in occasional patients with active rheumatic carditis treated with salicylates pulmonary edema developed which responded to phlebotomy.[12] Sutcliffe reported the case of a patient with rheumatic heart disease in whom pulmonary edema was noted after each of two courses of salicylates in the absence of any evidence for cardiac failure.[13] Granville-Grossman first reported salicylate-related pulmonary edema in a man without known heart disease. However, the pulmonary edema occurred only after forced alkaline diuresis suggesting that volume overload may have played a role.[14] Subsequently, the cases of three salicylate-intoxicated patients were reported[7,8] who presented with pulmonary edema and no apparent heart disease or clinical evidence of congestive heart failure. Pulmonary capillary wedge pressures, however, were not obtained so that a noncardiac cause was poorly documented. Hrnicek's case report[9] was the first to document normal pulmonary vascular pressures in a case of salicylate pulmonary edema. In Anderson's review of 73 patients with salicylism, seven of the patients presented with pulmonary edema and in one of these hemodynamic monitoring showed a normal pulmonary capillary wedge pressure.[15]

Our patient was admitted with extreme hypoxia and pulmonary infiltrates considered to represent pulmonary edema. Aspiration pneumonitis could have mimicked the radiographic findings and clinical presentation. However, the absence of a history of aspiration or of visible vomitus, the rapid clearing shown on sequential chest radiograms without a course of antibiotics, and the absence of pulmonary pathogens made this diagnosis unlikely. The pulmonary edema was deemed noncardiogenic because of the low pulmonary capillary wedge pressure and salicylism was considered to be the primary precipitating factor because a fall in serum drug levels coincided with clinical improvement.

The mechanism by which salicylates induce pulmonary edema is uncertain. Increased plasma volume with resulting elevated left atrial pressure was suggested by Reid.[12] However, the findings of a low pulmonary capillary wedge pressure exclude this explanation. For the same reason the mechanism of salicylate induced "high output" failure suggested by animal[16] and human[17] studies lacks support.

Experiments in sheep provide evidence that salicylates may mediate pulmonary edema by damaging pulmonary vessel endothelium thereby increasing capillary permeability to fluid and protein.[18] Cannulated lymphatic channels draining the lungs of these animals show an increase in lymph flow and lymphatic protein content after intravenous infusion of acetylsalicylate. These events occur without accompanying changes in pulmonary vascular pressures. These results suggest that salicylates generated a capillary-alveolar membrane "leak" with transudation of intravascular fluid and protein into the alveolar space.

If pulmonary edema is produced through damage to pulmonary vascular membranes, the mechanism whereby salicylates generate these defects is speculative. Conceivably, they may directly stimulate the brain, triggering a massive sympathetic nervous system discharge similar to that postulated for neurogenic pulmonary edema.[19] In this schema the sympathetic stimulus may produce a pronounced but transient increase in pulmonary artery pressures which somehow alters capillary permeability. After the pulmonary edema is established, the vasospasm remits and pulmonary vascular pressures are low or normal.

Alternatively, it has been suggested that prostaglandins are involved in salicylate pulmonary edema.[18,20] Prostaglandins may play a role in the generation of increased systemic vascular permeability,[21] and may be involved in maintaining the integrity of the pulmonary microcirculation.[22] Salicylates, by inhibiting prostaglandin synthetase, may intercede unfavorably in prostaglandin bal-

ance and thereby disturb the membrane stabilization process. Support for this thesis exists in preliminary findings in animal studies which suggest that indomethacin (also a prostaglandin synthetase inhibitor) has aspirin-like qualities of increasing pulmonary lymph flow.[20]

In addition, platelets have been incriminated in the production of this syndrome. Human platelets have an endothelium protective role,[23] and since salicylates impair platelet function, capillary membrane support may be weakened.

Regardless of the specific cause of the pulmonary edema, it is important that clinicians be aware of this complication of salicylism because florid respiratory failure may obscure common clues to the underlying diagnosis. In the case presented here, there were clinical and laboratory points suggesting salicylate toxicity such as hyperpnea, disorientation, ketonuria, acid-base abnormality and prolonged prothrombin time. But in the setting of pulmonary edema these findings could have been attributed to hypoxia and resultant lactic acidosis, recent starvation and suspected alcoholism with impaired hepatic synthetic capabilities.

Recently, Anderson has shown that patients taking salicylates chronically may present with occult toxicity.[15] The mortality in these patients increases to 25 percent if the diagnosis is delayed. The case reported here underscores the urgency of recognizing the multiple fashions in which salicylism presents in order to diagnose it clearly and treat it rapidly. Noncardiogenic pulmonary edema must alert clinicians to the possibility of salicylate overdosage particularly when other clues to the diagnosis are obscured by respiratory failure.

REFERENCES

1. Adelson E, Brunn F: Pulmonary edema in the course of treatment of multiple sclerosis with prostigmine: A report of two cases. Ann Intern Med 30:838-842, 1949

2. Brunschwig A, Allen J, Owens F, et al: Alloxan in treatment of insulin producing islet cell carcinoma of pancreas. JAMA 124: 212-216, 1944

3. Steinberg AD, Karliner JS: The clinical spectrum of heroin pulmonary edema. Arch Intern Med 122:122-127, 1968

4. Schoenfeld MR: Acute pulmonary edema caused by barbiturate poisoning—A consideration of its genesis and therapy. Angiology 15:445-453, 1964

5. Tennant FS: Complications of propoxyphene abuse. Arch Intern Med 132:191-194, 1973

6. Goldman AL, Enquist RW: Methadone pulmonary edema. Chest 63:275-276, 1973

7. Davis PR, Burch RE: Pulmonary edema and salicylate intoxication (Letter). Ann Intern Med 80:553-554, 1974

8. Tashima CK, Rose M: Pulmonary edema and salicylates (Letter). Ann Intern Med 81:274-275, 1974

9. Hrnicek G, Skelton J, Miller W: Pulmonary edema and salicylate intoxication. JAMA 230:866-867, 1974

10. Harrison TR (Ed): Principles of Internal Medicine, 8th Ed. New York, McGraw-Hill Book Co, 1977, pp 700-701

11. Goodman LS, Gilman A (Eds): The Pharmacological Basis of Therapeutics, 5th Ed. New York, The Macmillan Publishing Co, 1975, p 326

12. Reid J, Watson RD, Sproull DH: The mode of action of salicylates in acute rheumatic fever. QJ Med 19:261-268, 1950

13. Sutcliffe J: Pulmonary edema due to salicylates. Br J Radiol 28:314-316, 1955

14. Granville-Grossman KL, Sergeant HGS: Pulmonary edema due to salicylate intoxication. Lancet 1:575-577, 1960

15. Anderson RJ, Potts DE, Gabow PA, et al: Unrecognized adult salicylate intoxication. Ann Intern Med 85:745-748, 1976

16. Tenney SM, Miller RM: The respiratory and circulatory actions of acetylsalicylate. Am J Med 19:498-508, 1955

17. Alexander WD, Smith G: Disadvantageous circulatory effects of salicylate in rheumatic fever. Lancet 1:768-771, 1962

18. Bowers RE, Brigham KL, Owen PJ: Salicylate pulmonary edema: The mechanism in sheep and review of the literaure. Am Rev Respir Dis 115:261-268, 1977

19. Theodore J, Robin ED: Speculations on neurogenic pulmonary edema (NPE) (Editorial). Am Rev Respir Dis 113:405-411, 1976

20. Staub NC (Ed): Lung Water and Solute Exchange. New York, Marcel Dekker, Inc, 1978, pp 262-263

21. Willoughby D: Effects of prostaglandins F_2 and E on vascular permeabiilty. J Path Bact 96:381-387, 1968

22. Vane J, Piper P: Release of prostaglandins by the lung and other organs. Ann NY Acad Sci 180:363-381, 1971

23. Johnson SA (Ed): The Circulating Platelet. New York, Academic Press, 1971